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(54) **METHOD OF TREATING PULMONARY ARTERIAL HYPERTENSION**

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A61K 45/06 (2006.01)

(52) **U.S. Cl.**
CPC **A61K 31/4468** (2013.01); **A61K 45/06** (2013.01); **A61K 2300/00** (2013.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

(56) **References Cited**

PUBLICATIONS

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(57) **ABSTRACT**

Disclosed herein are compositions and methods for the treatment of pulmonary hypertension, including pulmonary arterial hypertension. The methods include administering to a patient in need thereof an effective amount of cinitapride or derivative thereof. The compositions include an effective amount of cinitapride or derivative thereof, in some instances combined with one or more additional agents for the treatment of pulmonary hypertension.

13 Claims, 10 Drawing Sheets

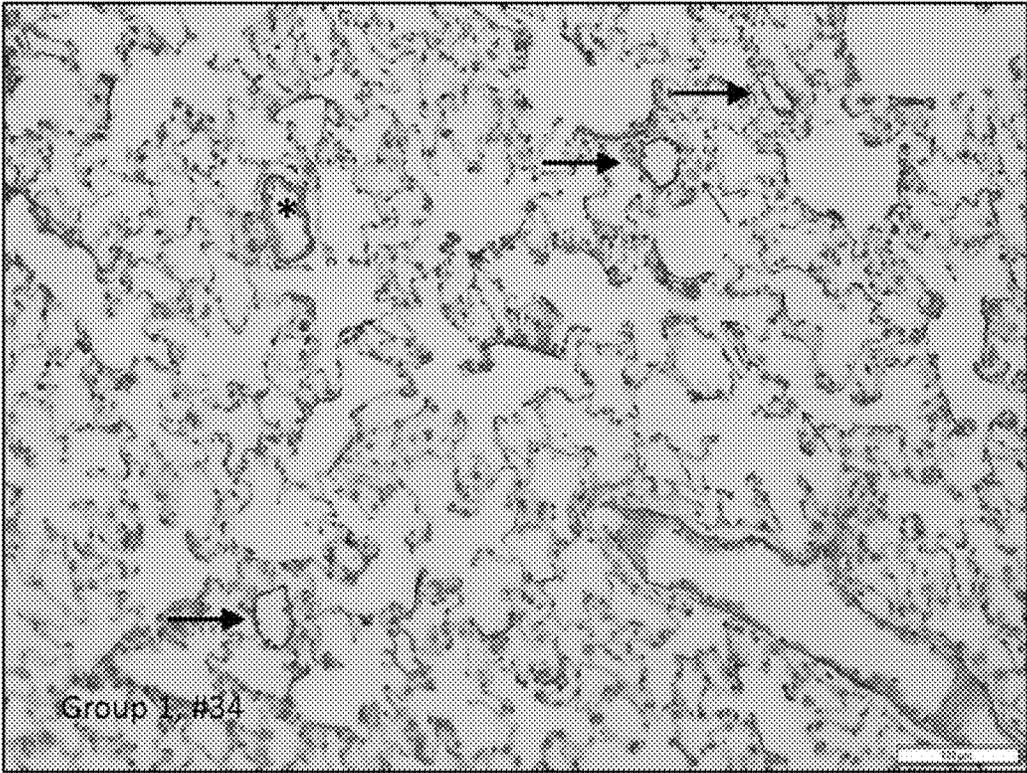


FIGURE 1

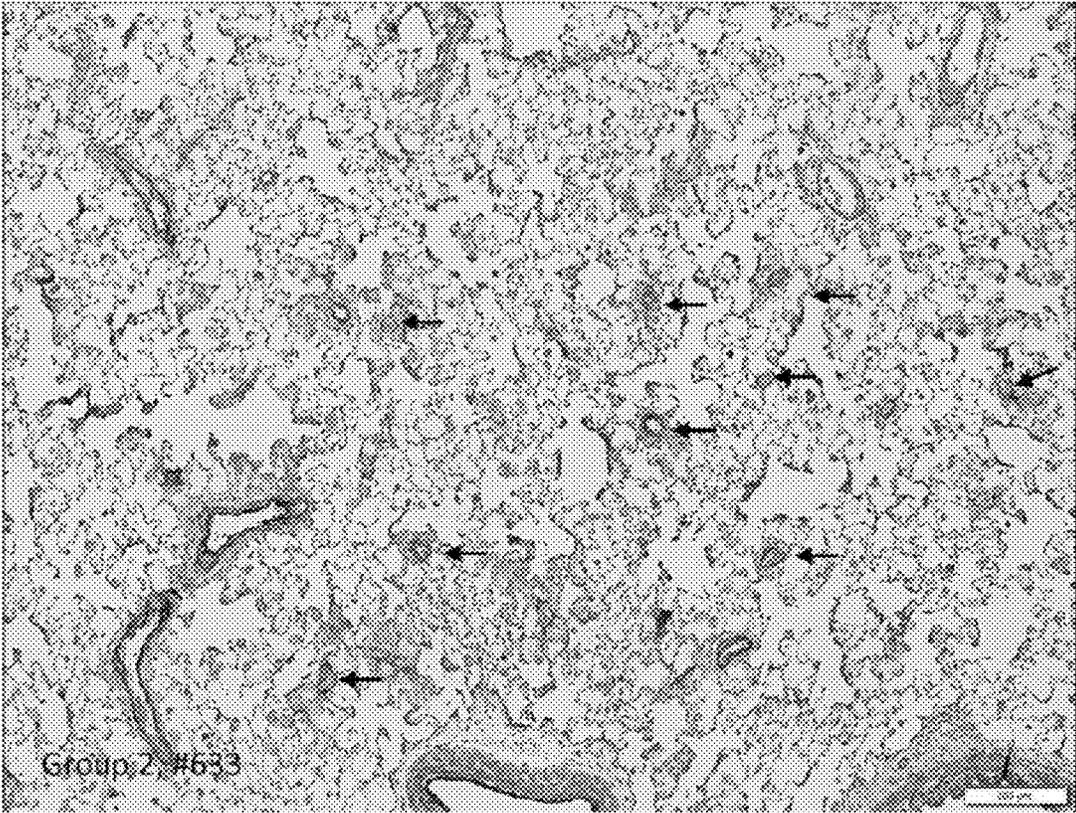


FIGURE 2

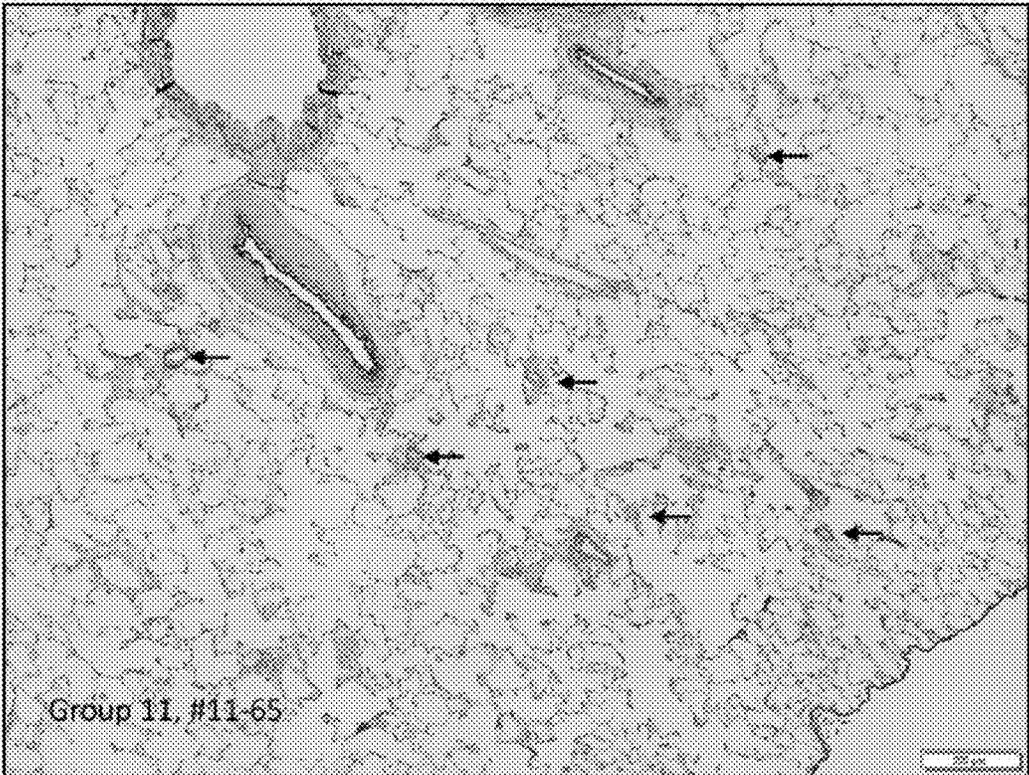


FIGURE 3

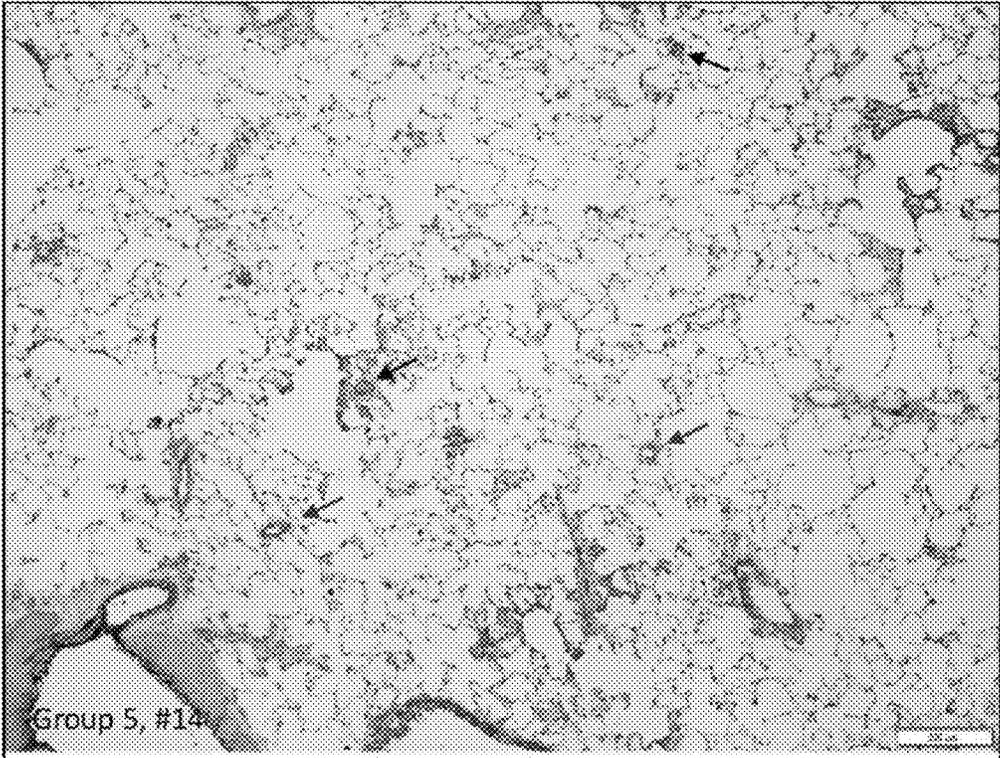


FIGURE 4

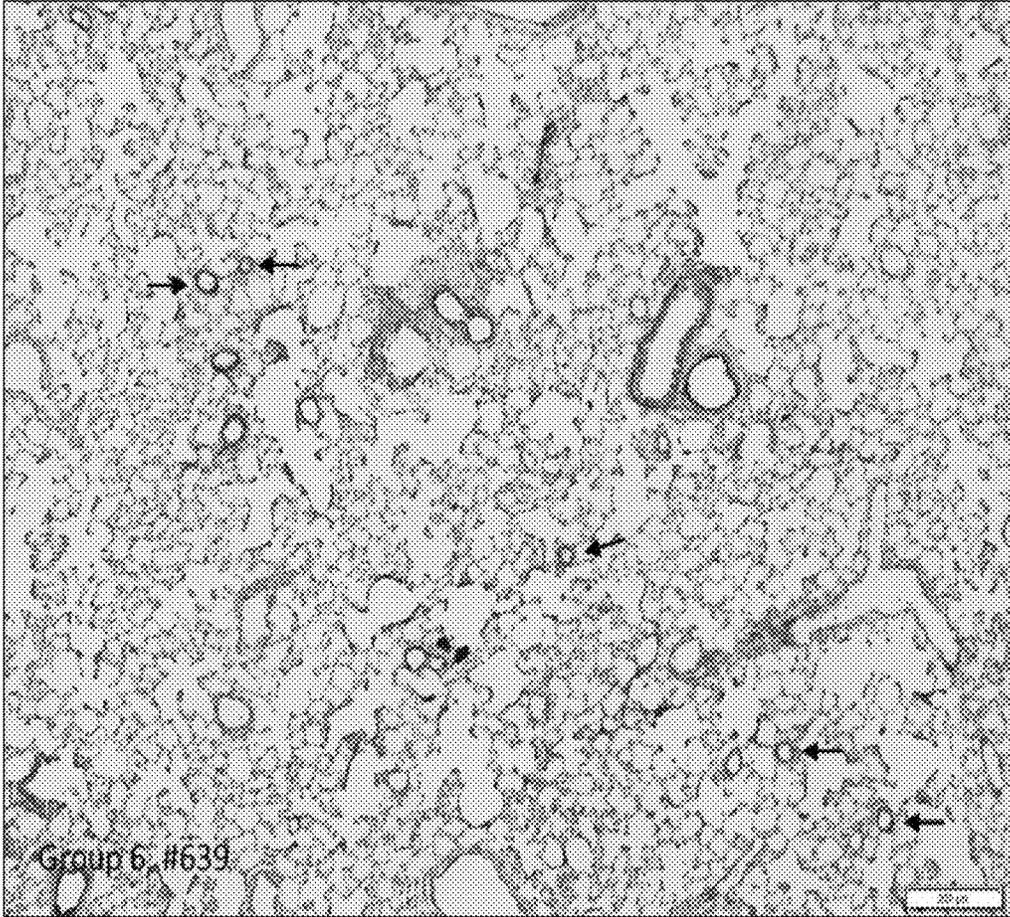


FIGURE 5

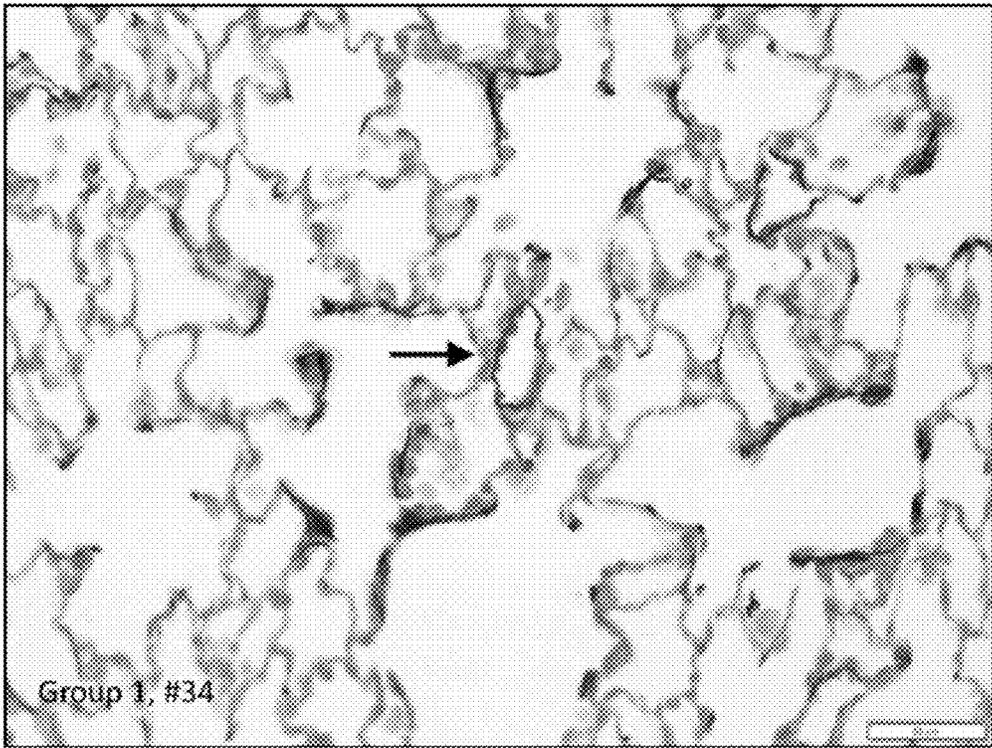


FIGURE 6

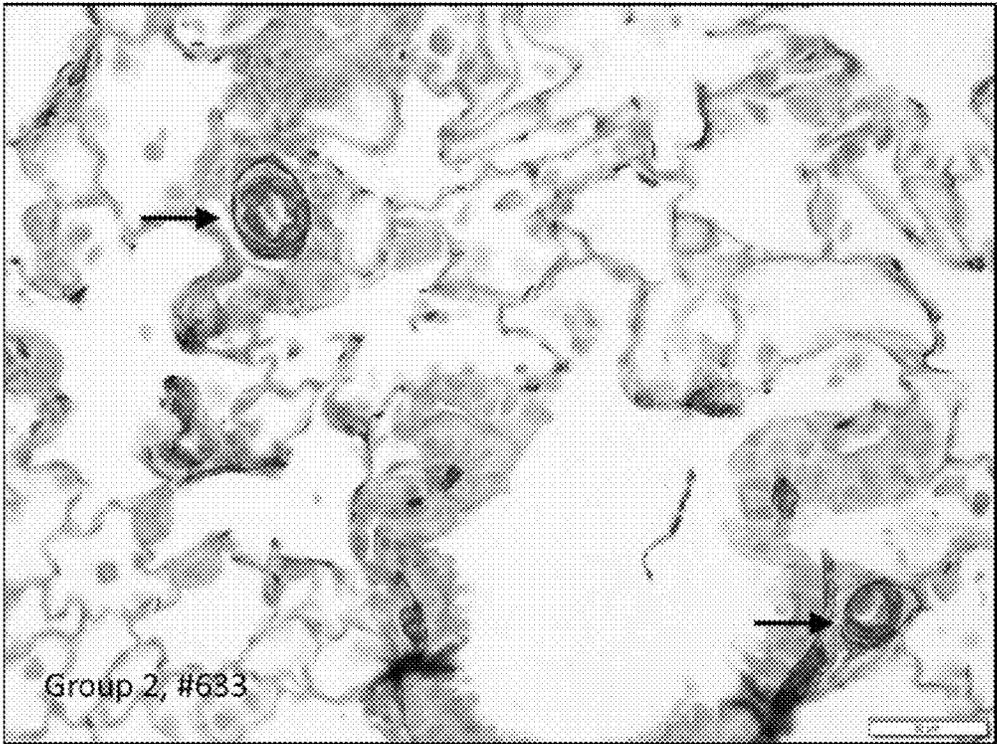


FIGURE 7

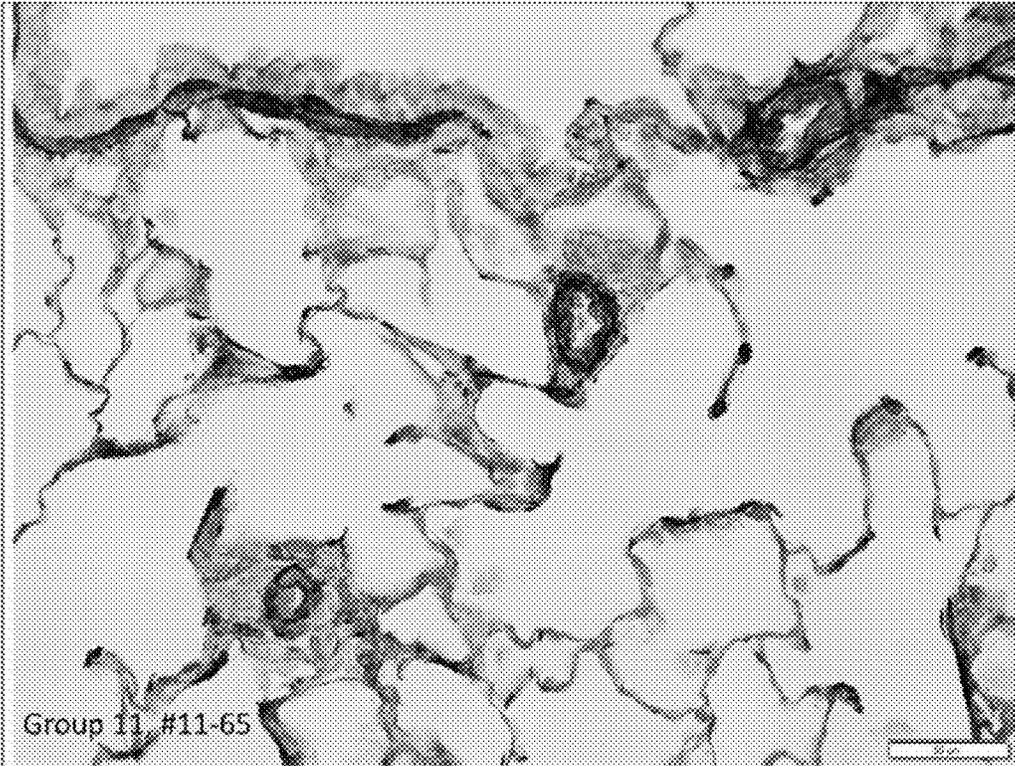


FIGURE 8



FIGURE 9

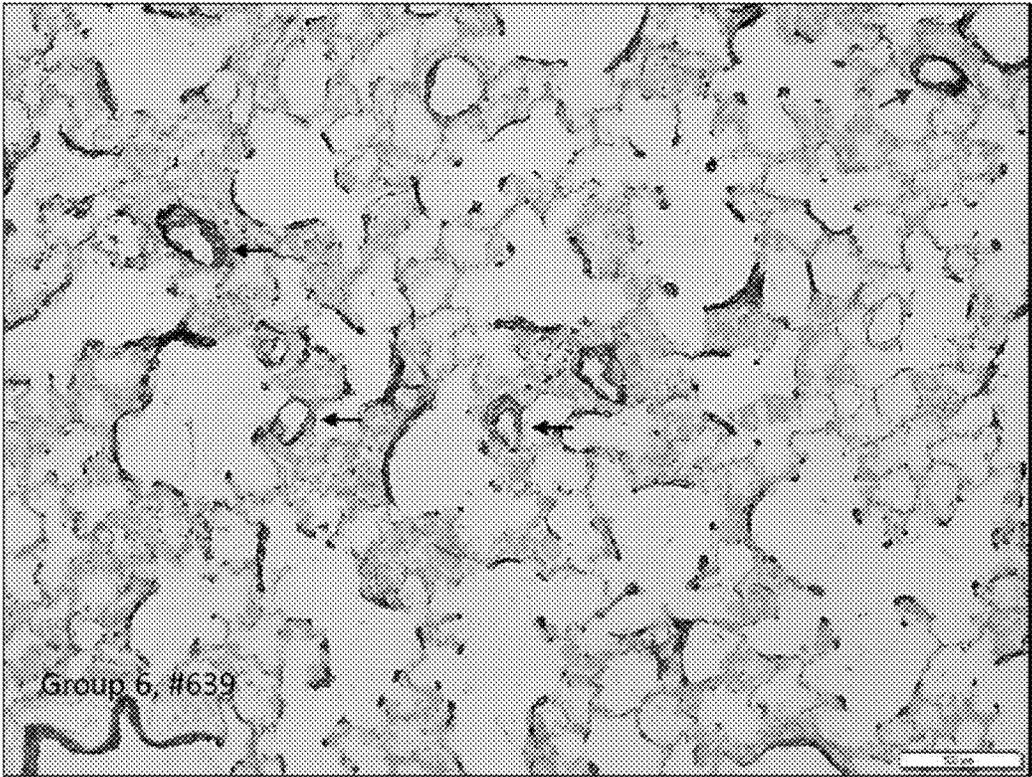


FIGURE 10

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METHOD OF TREATING PULMONARY ARTERIAL HYPERTENSION

CROSS REFERENCE TO RELATED APPLICATION

This application claims the benefit of Indian Application IN 201621027225, filed on Aug. 9, 2016, the contents of which are incorporated herein in its entirety.

FIELD OF THE INVENTION

The present invention relates to a method of treatment of pulmonary hypertension, including pulmonary arterial hypertension, by administering cinitapride either alone or optionally in combination with one or more other agents. The present invention also pertains to compositions and kits useful for the treatment of pulmonary arterial hypertension in humans containing cinitapride or derivative thereof, alone or in combination with one or more drugs.

BACKGROUND

Pulmonary arterial hypertension (PAH), one of the five types of pulmonary hypertension (PH), is a life-threatening disease characterized by pulmonary vascular remodeling that leads to increased pulmonary vascular resistance and pulmonary arterial pressure, most often resulting in right-side heart failure. It is a progressive condition characterized by elevated pulmonary arterial pressures leading to right ventricular (RV) failure. It is defined at cardiac catheterization as a mean pulmonary artery pressure of 25 mm Hg or more. The most common symptom associated is breathlessness, with impaired exercise capacity as a hallmark of the disease.

PAH is associated with significant morbidity and mortality. It is caused by complex pathways that culminate in structural and functional alterations of the pulmonary circulation and increases in pulmonary vascular resistance and pressure. Many mechanisms can lead to elevation of pulmonary pressures. In PAH, progressive narrowing of the pulmonary arterial bed results from an imbalance of vasoactive mediators, including prostacyclin, nitric oxide, and endothelin-1. This leads to an increased right ventricular afterload, right heart failure, and premature death. Diverse genetic, pathological, or environmental triggers stimulate PAH pathogenesis culminating in vasoconstriction, cell proliferation, vascular remodeling, and thrombosis. Current concepts suggest that PAH pathogenesis involves three primary processes: vasoconstriction, cellular proliferation/vascular remodeling, and thrombosis.

The molecular mechanism underlying PAH pathophysiology is not known yet, but it is believed that the endothelial dysfunction results in a decrease in the synthesis of endothelium-derived vasodilators such as nitric oxide and prostacyclin. Moreover, stimulation of the synthesis of vasoconstrictors such as thromboxane and vascular endothelial growth factor (VEGF) results in a severe vasoconstriction and smooth muscle and adventitial hypertrophy characteristic of patients with PAH.

Between 11% and 40% of patients with Idiopathic pulmonary arterial hypertension [IPAH] and 70% of patients with a family history of PAH carry a mutation in the gene encoding bone morphogenetic receptor-2 (BMPR2). However, penetrance is low, carriers have a 20% lifetime risk of developing pulmonary hypertension. Therefore, "multiple hits" are probably needed for the development of PAH. In

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pulmonary hypertension associated with left heart disease (PH-LHD), raised left atrial pressures result in secondary elevation of pulmonary pressure. In pulmonary hypertension owing to lung disease or hypoxia (PH-Lung), raised pulmonary arterial pressures result from mechanisms such as vascular destruction and hypoxic vasoconstriction. In chronic thromboembolic pulmonary hypertension [CTEPH], mechanical obstruction of the pulmonary vascular bed, is the primary process. Incidences are estimated to be 1-3.3 per million per year for IPAH and 1.75-3.7 per million per year for CTEPH; the prevalence of PAH is estimated at 15-52 per million. Pulmonary hypertension is more common in severe respiratory and cardiac disease, occurring in 18-50% of patients assessed for transplantation or lung volume reduction surgery, and in 7-83% of those with diastolic heart failure.

While there is currently no cure for PAH significant advances in the understanding of the pathophysiology of PAH have led to the development of several therapeutic targets. Besides conservative therapeutic strategies such as anticoagulation and diuretics, the current treatment paradigm for PAH targets the mediators of the three main biologic pathways that are critical for its pathogenesis and progression: (1) endothelin receptor antagonists inhibit the upregulated endothelin pathway by blocking the biologic activity of endothelin-1; (2) phosphodiesterase-5 inhibitors prevent breakdown and increase the endogenous availability of cyclic guanosine monophosphate, which signals the vasorelaxing effects of the down regulated mediator nitric oxide; and (3) prostacyclin derivatives provide an exogenous supply of the deficient mediator prostacyclin.

There are various drugs approved for the treatment of PAH: inotropic agents such as digoxin aids in the treatment by improving the heart's pumping ability. Nifedipine (Procardia) and Diltiazem (Cardizem) act as vasodilators and lowers pulmonary blood pressure and may improve the pumping ability of the right side of the heart

Bosentan (Tracleer), ambrisentan (Letairis), macitentan (Opsumit), etc. are dual endothelin receptor antagonist that help to block the action of endothelin, a substance that causes narrowing of lung blood vessels. There are others which dilate the pulmonary arteries and prevent blood clot formation. Examples of such drugs are Epoprostenol (Veletri, Flolan), treprostinil sodium (Remodulin, Tyvaso), iloprost (Ventavis); PDE 5 inhibitors such as Sildenafil (Revatio), tadalafil (Adcirca), relax pulmonary smooth muscle cells, which leads to dilation of the pulmonary arteries.

In addition to these established current therapeutic options, a large number of potential therapeutic targets are being investigated. These novel therapeutic targets include soluble guanylyl cyclase, phosphodiesterases, tetrahydrobiopterin, 5-hydroxytryptamine (serotonin) receptor 2B, vasoactive intestinal peptide, receptor tyrosine kinases, adrenomedullin, rho kinase, elastases, endogenous steroids, endothelial progenitor cells, immune cells, bone morphogenetic protein and its receptors, potassium channels, metabolic pathways, and nuclear factor of activated T cells.

Despite a certain success achieved in recent years, many patients with PAH are not adequately managed with existing therapies.

It is an object of the invention to provide a novel therapeutic method for the treatment of pulmonary hypertension, including pulmonary arterial hypertension.

It is an object of the invention to provide novel compositions for the treatment of pulmonary hypertension, including pulmonary arterial hypertension.

It is an object of the invention to provide a novel therapeutic method for the treatment of pulmonary hypertension, including pulmonary arterial hypertension, using cinitapride.

It is an object of the invention to provide novel compositions for the treatment of pulmonary hypertension, including pulmonary arterial hypertension, containing cinitapride.

SUMMARY

Disclosed herein are methods for treating pulmonary hypertension, for instance, pulmonary arterial hypertension, in patients in need thereof. In some instances, the methods include at least partial reduction of the symptoms associated with pulmonary hypertension, and in some instances include completed elimination of the symptoms associated with pulmonary hypertension. The methods include the use of cinitapride or a derivative thereof for the treatment of pulmonary hypertension. Also disclosed herein are compositions for the treatment of hypertension, wherein the compositions include cinitapride or a derivative thereof.

The details of one or more embodiments are set forth in the descriptions below. Other features, objects, and advantages will be apparent from the description and from the claims.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1: Vehicle group. The rats administered only DMSO shows normal pulmonary inflammatory cells. The black arrows point to normal, non-muscularized arterioles.

FIG. 2: Control group. The administration of monocrotaline and vehicle showed marked vascular smooth muscle hypertrophy. Arrows point to numerous partially or fully muscularized arterioles, which are readily visible at low magnification.

FIG. 3: Sildenafil treatment group. The sildenafil at dose of 30 mg/kg was administered after monocrotaline induction. The prominence and wall thickness of these small, muscularized arterioles (arrows) is similar compared to monocrotaline followed by vehicle.

FIG. 4: Cinitapride treatment group 1. The cinitapride at dose of 0.15 mg/kg was administered after monocrotaline induction. The treatment group showed mild vascular smooth muscle hypertrophy compared to control group. The wall thicknesses are often less (red arrows) than that compared to those with marked hypertrophy.

FIG. 5: Cinitapride treatment group 2. The cinitapride at dose of 0.45 mg/kg was administered after monocrotaline induction. The treatment group showed mild vascular smooth muscle hypertrophy compared to control group. The wall thicknesses are often less (red arrows) than that compared to those with marked hypertrophy.

FIG. 6: Vehicle group. DMSO showing a non-muscularized arteriole (arrow).

FIG. 7: Control group. The administration of monocrotaline followed by vehicle showed two fully muscularized arterioles (arrows).

FIG. 8: Sildenafil treatment group. The sildenafil at dose of 30 mg/kg was administered after monocrotaline induction. The thickness and extent of the muscularization of these arterioles is similar to animals induced with MCT followed by vehicle.

FIG. 9: Cinitapride treatment group 1. The cinitapride at dose of 0.15 mg/kg was administered after monocrotaline induction. The treatment group showed two partially mus-

cularized arterioles showing that these smaller arterioles are similar in thickness from a non-MCT induced animal vehicle control group.

FIG. 10: Cinitapride treatment group 2. The cinitapride at dose of 0.45 mg/kg was administered after Monocrotaline induction. The treatment group showed two partially muscularized arterioles showing that these smaller arterioles are similar in thickness from a non-MCT induced animal vehicle control group.

DETAILED DESCRIPTION

Before the present methods and systems are disclosed and described, it is to be understood that the methods and systems are not limited to specific synthetic methods, specific components, or to particular compositions. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

As used in the specification and the appended claims, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise. Ranges may be expressed herein as from “about” one particular value, and/or to “about” another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent “about,” it will be understood that the particular value forms another embodiment. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint.

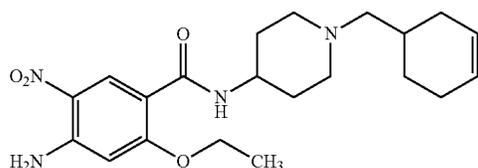
“Optional” or “optionally” means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances where it does not.

Throughout the description and claims of this specification, the word “comprise” and variations of the word, such as “comprising” and “comprises,” means “including but not limited to,” and is not intended to exclude, for example, other additives, components, integers or steps. “Exemplary” means “an example of” and is not intended to convey an indication of a preferred or ideal embodiment. “Such as” is not used in a restrictive sense, but for explanatory purposes.

Disclosed are components that can be used to perform the disclosed methods and systems. These and other components are disclosed herein, and it is understood that when combinations, subsets, interactions, groups, etc. of these components are disclosed that while specific reference of each various individual and collective combinations and permutation of these may not be explicitly disclosed, each is specifically contemplated and described herein, for all methods and systems. This applies to all aspects of this application including, but not limited to, steps in disclosed methods. Thus, if there are a variety of additional steps that can be performed it is understood that each of these additional steps can be performed with any specific embodiment or combination of embodiments of the disclosed methods.

Cinitapride is a benzamide class gastroprokinetic agent and anti-ulcer agent which act as agonist of the 5-HT₁ and 5-HT₄ receptors and as an antagonist of the 5-HT₂ receptors, it is used in the treatment of gastrointestinal disorders associated with motility disturbances such as gastroesophageal reflux disease, non-ulcer dyspepsia and delayed gastric emptying. Cinitapride is rapidly absorbed following oral administration. Cinitapride is chemically represented as—

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Cinitapride is indicated for the treatment of gastrointestinal disorders associated with motility disturbances such as gastroesophageal reflux disease, non-ulcer dyspepsia and delayed gastric emptying.

5-HT_{2A} is expressed widely throughout the central nervous system (CNS). It is expressed near most of the serotonergic terminal rich areas, including neocortex (mainly prefrontal, parietal, and somatosensory cortex) and the olfactory tubercle. Especially, high concentrations of this receptor on the apical dendrites of pyramidal cells in layer V of the cortex may modulate cognitive processes, working memory and attention. In the periphery, it is highly expressed in platelets and many cell types of the cardiovascular system, in fibroblasts, and in neurons of the peripheral nervous system. Additionally, 5-HT_{2A} mRNA expression has been observed in human monocytes.

Physiological processes mediated by the receptor include: CNS: neuronal excitation, behavioral effects, learning and anxiety

Smooth muscle: contraction (in gastrointestinal tract & bronchi)

Vasoconstriction/vasodilation

Platelets: aggregation

Activation of the 5-HT_{2A} receptor with 1-[2,5-dimethoxy-4-iodophenyl]-2-amino propane hydrochloride produces potent anti-inflammatory effects in several tissues including cardiovascular and gut. Other 5-HT_{2A} agonists like LSD also have potent anti-inflammatory effects against TNF-alpha-induced inflammation.

Activation of the 5-HT_{2A} receptor in hypothalamus causes increases in hormonal levels of oxytocin, prolactin, ACTH, corticosterone, and renin.

Role in memory

Unless specified to the contrary, the term "cinitapride" embraces both the free base and pharmaceutically acceptable salts thereof.

Pharmaceutically acceptable salts are salts that retain the desired biological activity of the parent compound and do not impart undesirable toxicological effects. Examples of such salts are acid addition salts formed with inorganic acids, for example, hydrochloric, hydrobromic, sulfuric, phosphoric, and nitric acids and the like; salts formed with organic acids such as acetic, oxalic, tartaric, succinic, maleic, fumaric, gluconic, citric, malic, methanesulfonic, p-toluenesulfonic, naphthalenesulfonic, and polygalacturonic acids, and the like; salts formed from elemental anions such as chloride, bromide, and iodide; salts formed from metal hydroxides, for example, sodium hydroxide, potassium hydroxide, calcium hydroxide, lithium hydroxide, and magnesium hydroxide; salts formed from metal carbonates, for example, sodium carbonate, potassium carbonate, calcium carbonate, and magnesium carbonate; salts formed from metal bicarbonates, for example, sodium bicarbonate and potassium bicarbonate; salts formed from metal sulfates, for example, sodium sulfate and potassium sulfate; and salts formed from metal nitrates, for example, sodium nitrate and potassium nitrate. Pharmaceutically acceptable and non-pharmaceutically acceptable salts may be prepared using

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procedures well known in the art, for example, by reacting a sufficiently basic compound such as an amine with a suitable acid comprising a physiologically acceptable anion. Alkali metal (for example, sodium, potassium, or lithium) or alkaline earth metal (for example, calcium) salts of carboxylic acids can also be made. Pharmaceutically acceptable cations include the cationic component of the acids listed above. Pharmaceutically acceptable anions include the anionic component of the bases listed above.

The term "treating" or "treatment" as used herein comprises a treatment relieving, reducing or alleviating at least one symptom in a subject or effecting a delay of progression of a disease. For example, treatment can be the diminishment of one or several symptoms of a disorder or complete eradication of pulmonary arterial hypertension. Within the meaning of the present invention, the term "treat" also includes to arrest, delay the onset (i.e., the period prior to clinical manifestation of a disease) and/or reduce the risk of developing or worsening a disease. The term "combination" as used herein, defines either a fixed combination in one dosage unit form, a non-fixed combination or a kit containing individual parts for combined administration.

Pulmonary hypertension can be classified as either primary or secondary. When the arterial hypertension is not accompanied or caused by another underlying heart or lung disease or condition, it is called primary pulmonary arterial hypertension. When the arterial hypertension is triggered by another disease state, it is designated secondary arterial pulmonary hypertension. Exemplary conditions which can cause secondary pulmonary hypertension include congenital heart defects, ventricular or atrial septal defects/holes, which are in some cases called Eisenmenger complex, as well as valve conditions such as stenosis.

Pulmonary hypertension can be associated with left heart disease, or right heart disease. In some embodiments, cinitapride (or a derivative thereof) can be used to treat pulmonary hypertension associated with left heart disease, whereas in other embodiments, cinitapride (or a derivative thereof) can be used to treat pulmonary hypertension associated with right heart disease. In further embodiments, cinitapride (or a derivative thereof) can be used to treat pulmonary hypertension associated with both right and left heart disease. Cinitapride can be used to treat patients with sporadic idiopathic PAH, heritable PAH, as well as PAH due to disease of small pulmonary muscular arterioles.

Disclosed herein are methods for treating patients with pulmonary arterial hypertension. The hypertension may be mild (resting arterial pressure between 14-25 mm Hg) or complete (resting arterial pressure greater than 25 mm Hg). The patient to be treated may have a pulmonary arterial pressure greater than 14 mm Hg, greater than 16 mm Hg, greater than 18 mm Hg, greater than 20 mm Hg, greater than 22 mm Hg, greater than 24 mm Hg, greater than 26 mm Hg, greater than 28 mm Hg, greater than 30 mm Hg, greater than 32 mm Hg, greater than 34 mm Hg, greater than 36 mm Hg, greater than 38 mm Hg, or greater than 40 mm Hg.

In some embodiments, cinitapride (or a derivative thereof) is administered to a patient (which may be a human or other mammal) in an amount sufficient to cause at least a 5%, 10%, 15%, 20%, 25%, 30%, 35%, or 40% reduction in resting arterial pressure relative to the pulmonary arterial pressure prior to commencing treatment. In some instances, cinitapride (or a derivative thereof) is administered at a dose effective such that the patient's final resting arterial pressure is about 25 mm Hg, about 24 mm Hg, about 23 mm Hg, about 22 mm Hg, about 21 mm Hg, about 20 mm Hg, about 19 mm Hg, about 18 mm Hg, about 17 mm Hg, about 16 mm

Hg, about 15 mm Hg, or about 14 mm Hg. In certain embodiments, cinitapride (or a derivative thereof) is administered in combination with other agents, as described below, to achieve these therapeutic outcomes.

Pulmonary hypertension can be characterized by a pulmonary blood pressure greater than about 25 mm Hg at rest, and 30 mm Hg during exercise. Normal pulmonary arterial pressure is about 14 mm Hg at rest. In certain embodiments, cinitapride (or a derivative thereof) can be used to treat patients having a resting pulmonary arterial pressure of at least 20 mm Hg, at least 25 mm Hg, at least 30 mm Hg, at least 35 mm Hg, at least 40 mm Hg, at least 45 mm Hg, at least 50 mm Hg, at least 55 mm Hg, or at least 60 mm Hg.

In some instances, the cinitapride may be administered to a patient a single time, while in other cases cinitapride can be administered using an intervallic dosing regimen. For instance, cinitapride may be administered once, twice, or three times a day for a period at least 1 week, for example 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 20 weeks, 40 weeks, or 52 weeks. In some instances, cinitapride administration can be suspended for some period of time (e.g., 1, 2, 3, 4, 6, 8, 10, 20, 40 or 52 weeks) followed by another period of administration.

In some instances, an initial dosage (higher dose, relative to maintenance dose) and maintenance doses (lower dose, relative to initial dose) may be specified. For instance, an initial dosage may be administered over the course of 1, 3, 5, 7, 10, 14, 21 or 28 days, followed by a maintenance dosage which is administered for the duration of the treatment. In some instances, the cinitapride can be administered to the patient using an interval greater than a day. For instance, the cinitapride can be administered once every other day, once every third day, once a week, once every two weeks, once every four weeks, once a month, once every other month, once every third month, once every six months, or once a year. In some instance injectable formulations, such as depot formulations, are suitable for dosing regimens with extended periods in between administration, however, oral formulations can also be used in such systems.

The dosage and dosage regimen may be calculated per kg body weight. The dosage regimen may vary from a day to a month. Preferably, the composition as contemplated by the invention may be administered at least once, twice or thrice a day in the dosing range from 0.05 mg to about 20 mg per day, 0.1 mg to about 10 mg per day, 0.5 mg to about 10 mg per day, 0.5 mg to about 5 mg per day, 1 mg to about 5 mg per day, or as per the requirement of the patient to be treated. For instance, cinitapride may be administered at a dose of 1 mg, given three times a day, at a dose of 2 mg, given three times a day, at a dose of 3 mg, given three times a day, at a dose of 4 mg, given three times a day, at a dose of 5 mg, given three times a day, at a dose of 1 mg, given two times a day, at a dose of 2 mg, given two times a day, at a dose of 3 mg, given two times a day, at a dose of 4 mg, given two times a day, or at a dose of 5 mg, given two times a day.

In some instances, the cinitapride (or a derivative thereof) may be administered to a patient a single time, while in other cases cinitapride (or a derivative thereof) can be administered using an intervallic dosing regimen. For instance, cinitapride (or a derivative thereof) may be administered once, twice, or three times a day for a period at least 1 week, for example 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 20 weeks, 40 weeks, or 52 weeks. In some instances, cinitapride (or a derivative thereof) administration can be suspended for some period of time (e.g., 1, 2, 3, 4, 6, 8, 10, 20, 40 or 52 weeks) followed by another period of administration.

Preferably, cinitapride (or a derivative thereof) may be provided in the form of a pharmaceutical composition such as but not limited to, unit dosage forms including tablets, capsules (filled with powders, pellets, beads, mini-tablets, pills, micro-pellets, small tablet units, multiple unit pellet systems (MUPS), disintegrating tablets, dispersible tablets, granules, and microspheres, multiparticulates), sachets (filled with powders, pellets, beads, mini-tablets, pills, micro-pellets, small tablet units, MUPS, disintegrating tablets, dispersible tablets, granules, and microspheres, multiparticulates), powders for reconstitution, transdermal patches and sprinkles, however, other dosage forms such as controlled release formulations, lyophilized formulations, modified release formulations, delayed release formulations, extended release formulations, pulsatile release formulations, dual release formulations and the like. Liquid or semisolid dosage form (liquids, suspensions, solutions, dispersions, ointments, creams, emulsions, microemulsions, sprays, patches, spot-on), injection preparations, parenteral, topical, inhalations, buccal, nasal etc. may also be envisaged under the ambit of the invention.

In some instances, cinitapride (or a derivative thereof) can be administered by inhalation, for instance as a powder or aerosolizable formulation.

The bioavailability of the drug in a composition, depends on various attributes of the drug as well as the other inactive ingredients in the formulation. The particle size of the drug is one of such attribute that may affect the bioavailability of the drug, when administered to a patient. The particle size may thus be adjusted as per the requirements of the invention.

The inventors of the present invention have also found that the solubility properties of cinitapride (or a derivative thereof) may be improved by nanosizing thus leading to better bioavailability and dose reduction of the drug.

In one embodiment, cinitapride (or a derivative thereof) may be present in the form of nanoparticles which have an average particle size of less than 2000 nm, less than 1500 nm, less than 1000 nm, less than 750 nm, or less than 500 nm.

Suitable excipients may be used for formulating the dosage forms according to the present invention such as, but not limited to, surface stabilizers or surfactants, viscosity modifying agents, polymers including extended release polymers, stabilizers, disintegrants or super disintegrants, diluents, plasticizers, binders, glidants, lubricants, sweeteners, flavoring agents, anti-caking agents, opacifiers, antimicrobial agents, antifoaming agents, emulsifiers, buffering agents, coloring agents, carriers, fillers, anti-adherents, solvents, taste-masking agents, preservatives, antioxidants, texture enhancers, channeling agents, coating agents or combinations thereof.

In some instances, the cinitapride (or a derivative thereof) can be administered to the patient using an interval greater than a day. For instance, the cinitapride (or a derivative thereof) can be administered once every other day, once every third day, once a week, once every two weeks, once every four weeks, once a month, once every other month, once every third month, once every six months, or once a year. In some instance injectable formulations, such as depot formulations, are suitable for dosing regimens with extended periods in between administration, however, oral formulations can also be used in such systems.

In some embodiments, pulmonary arterial hypertension can be alleviated or treated by administration of cinitapride

(or a derivative thereof) in combination with one or more other drugs either simultaneously, sequentially, or separately.

Preferably, one or more standard of care drugs that may be envisaged under the scope of the present invention may comprise from categories of for the treatment of pulmonary hypertension such as, but not limited to phosphodiesterase inhibitors, endothelin receptor antagonist, Inotropic agents, and stimulators of soluble guanylate cyclase, such as riociguat.

Specifically, one or more standard of care drugs include but not limited to sildenafil, tadalafil, bosentan, ambrisentan, macitentan, nifedipine, diltiazem, digoxin. There are others which dilate the pulmonary arteries and prevent blood clot formation. Examples of such drugs are Epoprostenol (Veletri, Flolan), treprostinil sodium (Remodulin, Tyvaso), iloprost (Ventavis); PDE 5 inhibitors such as Sildenafil (Revatio), tadalafil (Adcirca), relaxes pulmonary smooth muscle cells, which leads to dilation of the pulmonary arteries.

The use of cinitapride may preferably be associated with one or more of the above referenced drugs as a combination therapy (either of the same functional class or other) depending on various factors like drug-drug compatibility, patient compliance and other such factors wherein the said combination therapy may be administered either simultaneously, sequentially, or separately for the treatment of PAH.

Cinitapride (or a derivative thereof) may be provided with one or more drugs in the form of a kit, wherein the kit includes cinitapride and at least one other drug, and instructions for their administration to a PAH patient.

In certain embodiments, the administration of cinitapride (or a derivative thereof), either alone or in combination with one or more drugs selected from but not limited to phosphodiesterase inhibitors such as sildenafil, tadalafil etc., endothelin receptor antagonist such as bosentan, macitentan etc. and stimulators of soluble guanylate cyclase such as riociguat. In certain embodiments, cinitapride (or a derivative thereof) can be co-administered with one or more additional agents effective to lower pulmonary hypertension. In some embodiments the co-administration includes a unitary dosage form containing cinitapride (or a derivative thereof) and at least one more agent. In other embodiments, cinitapride (or a derivative thereof) is administered separately from the other agent(s). The additional agent can be a PDE-5 inhibitor, for example, avanafil, lodenafil, mirodenafil, sildenafil, tadalafil, vardenafil, udenafil, zaprinast, or icariin. Other agents include calcium channel blockers like dihydropyridines (e.g., amlodipine, nifedipine) and diltiazem; prostacyclin pathway agonists such as epoprostenol, treprostinil, iloprost, and selexipag; endothelin receptor antagonists such as bosentan, macitentan, ambrisentan, and sitaxsentan; guanylate cyclase stimulators such as riociguat; diuretics; toprimate; fusadil; or anti-coagulants like warfarin.

It may be well appreciated by a person skilled in the art that the pharmaceutical composition comprising cinitapride in combination with one or more drugs may require specific dosage amounts and specific frequency of administrations specifically considering their individual established doses, the dosing frequency, patient adherence and the regimen adopted. As described herein, considering that there are

various parameters to govern the dosage and administration of the combination composition as per the present invention, it would be well acknowledged by a person skilled in the art to exercise caution with respect to the dosage, specifically, for special populations associated with other disorders.

EXAMPLES

The following examples are set forth below to illustrate the methods and results according to the disclosed subject matter. These examples are not intended to be inclusive of all aspects of the subject matter disclosed herein, but rather to illustrate representative methods, compositions, and results. These examples are not intended to exclude equivalents and variations of the present invention, which are apparent to one skilled in the art.

Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.) but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in ° C. or is at ambient temperature, and pressure is at or near atmospheric. There are numerous variations and combinations of reaction conditions, e.g., component concentrations, temperatures, pressures, and other reaction ranges and conditions that can be used to optimize the product purity and yield obtained from the described process. Only reasonable and routine experimentation will be required to optimize such process conditions.

Example 1—Pulmonary Arterial Hypertension Efficacy Model: Monocrotaline Rat

The studies were conducted for hemodynamic evaluation of cinitapride in anesthetized sprague dawley rats treated with monocrotaline (“MCT”) to induce pulmonary arterial hypertension. Sildenafil was used as an internal control to compare the effects of cinitapride.

The effects of cinitapride were evaluated in rats with monocrotaline induced pulmonary arterial hypertension using sildenafil as standard care treatment. Male Sprague-Dawley rats were orally administered vehicle cinitapride (0.3 or 0.9 mg/kg total daily dose, divided into a BID regimen given every day for 28 days starting on Day 1), or sildenafil (30 mg/kg, administered twice daily) (n=10 in each group). Rats received a single injection of monocrotaline (60 mg/kg, s.c.) on Study Day 1. On the twenty-eighth day following monocrotaline dosing, the rats were anesthetized with ketamine/xylazine for terminal monitoring of pulmonary and systemic arterial pressures along with heart rate.

Test Item:

Vehicle (0.5% Methylcellulose+0.2% Tween 80 in deionized water, Cinitapride (0.3 or 0.9 mg/kg total daily dose; Sildenafil (30 mg/kg, administered twice daily)

Route of Administration:

Oral

* is 0.5% methyl cellulose+0.2% Tween 80 in deionized water

Study Design:

The study was planned and conducted according to design depicted below in Table 1

TABLE 1

Study Design							
Group	Test Compound	Test Compound		Dose		Dose Days	No. of Male Rats
		Dose Level (mg/kg)	Conc. (mg/mL)	Volume (mL/kg)	Dose Route		
1	DMSO	NA	NA	1	SC	1	5
2	Vehicle	NA	NA	5	Oral	1-28	10
3	Cinitapride	0.15	0.03	5	Oral	1-28	10
4	Cinitapride	0.15	0.03	5			
		0.45	0.09	5	Oral	1-28	10
5	Sildenafil	0.45	0.09	5			
		30	6	5	Oral	1-28	10
		30	6	5			

Male Sprague-Dawley rats in groups 2 to 5 were administered 80 mg/kg of body weight of Monocrotaline in DMSO subcutaneously to induce PAH on day 1. The DMSO group (Group 1) received a single dose of DMSO subcutaneously on day 1. The vehicle group received 5 ml of vehicle every morning. The cinitapride as well as sildenafil groups were orally administered cinitapride (0.3 or 0.9 mg/kg total daily dose, divided into a BID regimen given every day for 28 days starting on Day 1), or sildenafil (30 mg/kg, administered twice daily). On the twenty-eighth day after monocrotaline dosing, the rats were anesthetized with ketamine/xylazine for terminal monitoring of pulmonary and systemic arterial pressures along with heart rate.

Later the animals were sacrificed and histopathological evaluation was performed to assess pulmonary arterioles for smooth muscle hypertrophy & muscularization of pulmonary arterioles.

The elastin/eosin stained lung section were examined microscopically and histopathological findings were recorded as smooth muscle hypertrophy of small arterioles and muscularization of pulmonary arterioles. The finding were recorded as 0 (normal), 1 (minimal), 2 (mild), 3 (moderate) or 4 (marked). Scoring smooth muscle hypertrophy in small pulmonary arterioles was based on the thickness of muscular wall & extent of finding (apparent no. of arterioles affected).

Observation:

There were differences in systolic and mean pulmonary arterial pressures after 28 days in rats treated with 0.9 mg/kg/day cinitapride compared to the vehicle group. Rats treated with cinitapride at this dose showed a reduction in systolic pulmonary arterial pressure.

There was also a dose-dependent beneficial effect with respect to right ventricular hypertrophy (as measured by RV/LV+S—Fulton's Index) in the cinitapride groups compared to vehicle.

When correcting RV (wt) by body weight, cinitapride showed a decrease ($p < 0.05$) in hypertrophy at the highest dose. No substantive differences in heart rate or mean arterial pressure were noted for rats treated with cinitapride compared to vehicle. Sildenafil also had a decrease in this hypertrophic index, respectively.

When considering overall mortality, pulmonary hemodynamics, and right ventricular hypertrophy—the oral administration of cinitapride (specifically at 0.9 mg/kg/day given BID) was the most effective at reducing monocrotaline-induced pulmonary hypertension in the rat. This cinitapride regimen was superior to the positive control (sildenafil) with regard to efficacy.

The smooth muscle hypertrophy was present in small arterioles of most animals administered Monocrotaline. The severity of smooth muscle hypertrophy was the greatest in animals administered Monocrotaline followed by vehicle. The Cinitapride administration at a dose of 0.15 mg/kg and 0.45 mg/kg twice daily following Monocrotaline administration substantially decreased presence of smooth muscle hypertrophy.

The mean hypertrophy scores were 0.2 in untreated animals, 2.7 in monocrotaline+vehicle treated, 1.9 and 2.1 in monocrotaline+cinitapride (0.15 and 0.45 bid respectively) treated animals. The results are depicted in FIGS. 1-5.

b) Muscularization of Pulmonary Arterioles:

The percentage of completely muscularized pulmonary arterioles were increased in all animals administered monocrotaline. Animals administered vehicle following MCT administration had the highest mean percentages of completely muscularized arterioles among all groups (52.1%).

Animals administered 0.45 mg/kg cinitapride twice daily following MCT administration had the greatest decrease in completely muscularized arterioles as indicated by the group mean percentage (38.2%). The results are depicted in FIGS. 6-10.

Results:

Body weights among the vehicle and treatment cohorts were not significantly different at Study Day 28. There were differences in systolic and mean pulmonary arterial pressures after 28 days in rats treated with 0.9 mg/kg/day cinitapride compared to the vehicle group.

Rats treated with cinitapride at this dose dependent reduction in systolic pulmonary arterial pressure. There was also a dose-dependent beneficial effect with respect to right ventricular hypertrophy (as measured by RV/LV+S—Fulton's Index) in the cinitapride groups (-10% and -25% at 0.3 and 0.9 mg/kg/day, respectively) compared to vehicle. The results are depicted in Table 2.

Parameter Mean ± SEM	Treatment Cohort (mg/kg)				
	DMSO (Without induction of PAH)	Vehicle	Cinitapride 0.3 per day bid	Cinitapride 0.9 per day bid	Sildenafil 60 per day bid
Systolic PAP (mmHg)	16 ± 2	60 ± 2	55 ± 8	45 ± 4	46 ± 7
Mean PAP (mmHg)	14 ± 2	46 ± 1	43 ± 5	37 ± 3	38 ± 6
MAP (mmHg)	84 ± 9	70 ± 6	77 ± 8	76 ± 2	69 ± 5
HR (bpm)	313 ± 13	274 ± 10	299 ± 17	295 ± 9	278 ± 21
Heart Weight (g)	1.17 ± 0.03	1.36 ± 0.05	1.17 ± 0.05*	1.10 ± 0.05**	1.24 ± 0.02
HW/BW	2.75 ± 0.07	4.43 ± 0.15	3.71 ± 0.20*	3.52 ± 0.16*	3.89 ± 0.17
LV Weight (g)	0.82 ± 0.01	0.78 ± 0.01	0.68 ± 0.04	0.70 ± 0.03	0.74 ± 0.02
RV Weight (g)	0.22 ± 0.02	0.46 ± 0.02	0.35 ± 0.02*	0.31 ± 0.03**	0.38 ± 0.02
Lung Weight (g)	1.65 ± 0.08	2.90 ± 0.53	2.36 ± 0.16	2.30 ± 0.20	2.36 ± 0.13
RV/LV + S	0.26 ± 0.02	0.59 ± 0.03	0.53 ± 0.04	0.45 ± 0.04	0.51 ± 0.03
RV/BW	0.50 ± 0.03	1.50 ± 0.06	1.14 ± 0.10	1.01 ± 0.11*	1.19 ± 0.09
Body Weight (Kg)	0.43 ± 0.01	0.31 ± 0.02	0.32 ± 0.02	0.32 ± 0.02	0.32 ± 0.01

When correcting RV (wt) by body weight, cinitapride showed a 33% decrease (p<0.05) in hypertrophy at the highest dose. No substantive differences in heart rate or mean arterial pressure were noted for rats treated with cinitapride compared to vehicle.

The results suggest that cinitapride activity in controlling or reducing PAH was found to be comparable among with Sildenafil activity.

Example 2: Process for Formulating the Cinitapride Composition According to the Invention

1. Prepare the binder solution by dissolving Povidone in purified water.
2. Sift Cinitapride, Microcrystalline cellulose, Lactose, Corn Starch and Hypromellose through specified mesh sieve.
3. Load the sifted materials of step 2 in a rapid mixer granulator and dry mix.
4. Granulate the dry mix by using the binder of step 1.
5. Dry and size the granules obtained in step 4.
6. Blend the dried sized granules with presifted Colloidal silicon dioxide and talc followed by lubrication with presifted magnesium stearate in a suitable blender.
7. Compress the lubricated blend into tablets using suitable tooling
8. Prepare the film coating solution by dispersing the opadry dry mix in purified water.
9. Coat the compressed tablets obtained in step 7 with the film coating dispersion prepared in step 8.

Example 3: Pharmaceutical Composition Prepared Using the Process in Example 2

Sr. No	Ingredients	Qty (mg/tab)
1.	Cinitapride	0.1-50
2.	Microcrystalline cellulose	75-200
3.	Lactose	75-200
4.	Povidone	4-16
5.	Corn Starch	10-45
6.	Purified water	Qs
7.	Hypromellose (HPMC K4M/K15 M/K100 M)	150-750

-continued

Sr. No	Ingredients	Qty (mg/tab)
8.	Colloidal silicon dioxide	1-6
9.	Talc	3-12
10.	Magnesium Stearate	3-12
11	Ready mix opadry	5-10
12	Purified water	Qs

Example 4: Process for Formulating the Cinitapride Composition According to the Invention

1. Prepare a slurry of maize starch in purified water.
2. Sift mannitol, Cinitapride, and the remaining part of maize starch through specified mesh size.
3. Load the shifted material of step 2 in a rapid mixer granulator and dry mix.
4. Granulate dry mix from step 3 with using starch paste of step 1.
5. Dry and size the granules obtained in step 4.
6. Blend the dried and sized granules with pre-shifted Starch 1500, Aerosil 200, and sodium stearyl fumarate in suitable blender.
7. Compress the blend of step 6 into tablets using suitable tooling.

Example 5: Pharmaceutical Composition Prepared Using the Process in Example 4

Sr. No.	Ingredients	Mg/tablet
1	Cinitapride	0.1-50
2	Mannitol	40-100
3	Maize starch	35-80
4	Pregelatinized starch (Starch 1500)	10-25
5	Colloidal silicone dioxide (Aerosil 200)	0.25-2.5
6	Sodium stearyl fumarate	1-5
7	Purified water	QS

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Example 6: Process for Formulating the Cinitapride Composition According to the Invention

1. Sift the Cinitapride, lactose anhydrous, hydroxyl propyl cellulose and colloidal silicon dioxide through specific mesh sieve.
2. Blend the sifted materials of step 1 in suitable blender for specified period of time
3. Blend dry mix of step 2 with pre-sifted Magnesium stearate.
4. Compress the dry blend of step 3 into tablets using suitable tooling

Example 7: Pharmaceutical Composition Prepared Using the Process in Example 6

Sr. no	Ingredients	Qty Mg/tablet
1.	Cinitapride	0.1-10
2.	Lactose anhydrous	10-100
3.	Hydroxy Propyl cellulose	20-80
4.	Colloidal silicon dioxide	0.1-2
5.	Magnesium stearate	0.1-2

The compositions and methods of the appended claims are not limited in scope by the specific compositions and methods described herein, which are intended as illustrations of a few aspects of the claims and any compositions and methods that are functionally equivalent are intended to fall within the scope of the claims. Various modifications of the compositions and methods in addition to those shown and described herein are intended to fall within the scope of the appended claims. Further, while only certain representative compositions and method steps disclosed herein are specifically described, other combinations of the compositions and method steps also are intended to fall within the scope of the appended claims, even if not specifically recited. Thus, a combination of steps, elements, components, or constituents may be explicitly mentioned herein or less, however, other combinations of steps, elements, components, and constituents are included, even though not explicitly stated. The term "comprising" and variations thereof as used herein is used synonymously with the term "including" and variations thereof and are open, non-limiting terms. Although the terms "comprising" and "including" have been used herein to describe various embodiments, the terms "consisting essentially of" and "consisting of" can be used in place of "comprising" and "including" to provide for more specific embodiments of the invention and are also disclosed. Other than in the examples, or where otherwise noted, all numbers expressing quantities of ingredients,

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reaction conditions, and so forth used in the specification and claims are to be understood at the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, to be construed in light of the number of significant digits and ordinary rounding approaches.

What is claimed is:

1. A method of treating pulmonary arterial hypertension (PAH) in a patient in need thereof, comprising administering to the patient in need of such treatment a composition comprising an effective amount of cinitapride or pharmaceutically acceptable salt thereof.

2. The method of claim 1, wherein the patient has a resting pulmonary arterial pressure greater than 24 mm Hg.

3. The method of claim 1, wherein the patient has a resting pulmonary arterial pressure greater than 40 mm Hg.

4. The method of claim 1, wherein cinitapride is administered in an amount effective to lower resting pulmonary arterial blood pressure at least 5% relative to the resting pulmonary arterial blood pressure prior to commencing the treatment.

5. The method of claim 1, wherein cinitapride is administered in an amount effective to lower resting pulmonary arterial blood pressure to a level no greater than 18 mm Hg.

6. The method of claim 1, wherein cinitapride is administered in a dose from 0.1 to 50 mg.

7. The method of claim 1, wherein cinitapride is administered once, twice, or three times a day.

8. The method of claim 7, wherein the cinitapride is administered in a total daily dosage of from 0.5 mg-10 mg.

9. The method of claim 1, wherein the composition is administered orally.

10. The method of claim 1, wherein the composition is administered parenterally.

11. The method of claim 1, further comprising administering at least one other agent effective to treat pulmonary arterial hypertension.

12. The method of claim 11, wherein the at least one other agent comprises a PDE-5 inhibitor, a calcium channel blocker, a prostacyclin pathway agonist, an endothelin receptor antagonist, a guanylate cyclase stimulators, an anti-coagulants, or a combination thereof.

13. The method of claim 12, wherein the at least one other agent comprises:

a PDE-5 inhibitor selecting from avanafil, lodenafil, mirodenafil, sildenafil, tadalafil, vardenafil, udenafil, zaprinast, or icariin; or

a prostacyclin pathway agonist selected from epoprostenol, treprostiniil, iloprost, or selexipag; or

an endothelin receptor antagonist selected from bosentan, macitentan, ambrisentan, or sitaxsentan.

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